

REMARKS

Applicants herein add new Claims 47-52. Support for these claims can be found throughout the Specification, for example, in Examples 1 and 2 on pages 65-66 and Figure 8, among other places. No new matter has been added.

Thus, Claims 26-52 are pending subsequent to entry of these amendments.

I. Nonstatutory Obviousness-Type Double Patenting

The Examiner rejected Claims 26-27, 29-31, 33-35 and 38-46 as allegedly being unpatentable over Claims 1-2, 8-10, 22-23 and 27 of U.S. Patent No. 6,471,968 (hereinafter "the '968 patent") in view of Tomalia et al., Agnew Chem. Int. Ed. Engl. 29, 138-175 (1990), as further evidenced by Zhou et al., J Controlled Release (1999) (Office Action, page 3).

Applicants respectfully disagree.

Nonetheless, without acquiescing to any of the Examiner's arguments and in order to further the prosecution of the present invention, Applicants herein agree to file a terminal disclaimer with regard to the '968 patent. Applicants believe that this renders the Examiner's nonstatutory obviousness-type double patenting rejection moot.

II. The Claims are Not Obvious

The Examiner rejected Claims 26-35 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tomalia et al., Agnew Chem. Int. Ed. Engl. 29, 138-175 (1990) (hereinafter "Tomalia et al.") and Zhou et al., Journal of Controlled Release (1999) (hereinafter "Zhou et al.") in view of Malik et al. (Proceed. Int'l Symp. Control. Rel. Bioact. Mater., 24: 107-108 (1997) hereinafter "Malik et al.") (Office Action page 5); and Claims 26-27 and 36-37 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tomalia et al. and Zhou et al., in view of U.S. Patent No. 5,714,166 (herein after "the '166 patent") (Office Action page 6).

Applicants respectfully disagree.

In rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of presenting a prima facie case of obviousness.¹ A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject

¹ See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

matter to a person of ordinary skill in the art.² An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art.³

The test for *prima facie* obviousness is consistent with legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). The Federal Circuit summarized the Supreme Court's holding in *KSR* that "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a **reason** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus., Ltd. v. Alphapharma Pty., Ltd.*, 06-1329, slip op. (Fed. Cir. June 28, 2007), at 13-14 (quoting *KSR*, 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR*, 127 S. Ct. at 1731. The *KSR* Court upheld the secondary considerations of non-obviousness, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

Applicants contend that the cited references, individually or in combination, do not teach, suggest nor enable each element of the claimed invention, actually lead one of ordinary skill in the art away from the claimed invention, and do not provide a reasonable expectation of success for carrying out the claimed invention to one of ordinary skill in the art. Moreover, Applicants submit that the Examiner has improperly utilized hindsight reconstruction of the claimed invention in an effort to support the allegation that the claimed invention is *prima facie* obvious.

A) The Claims are Not Obvious over Tomalia et al. and Zhou et al in View of Malik et al.

1) The Cited References Do Not Teach, Disclose Nor Enable Each Element of the Claimed Invention

² In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993).

³ In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Tomalia et al. does not teach or disclose dendrimer acetylation.

The Examiner acknowledges that “Tomalia et al does not teach acylation of dendrimers” and that “Tomalia et al and Zhou et al do not teach chemotherapeutic agents such as the platinum complex, cisplatin” (Office Action page 5 and 6).

Moreover, Malik et al. does not teach, describe or suggest a composition comprising an acetylated dendrimer.

Additionally, the cited references do not teach, disclose or enable a composition comprising a dendrimer comprising an acetylated generation 5 (G5) polyamideamine (PAMAM) or polypropylamine (POPAM) dendrimer comprising one or more functional groups, wherein at least one of said functional groups comprises a therapeutic agent, wherein the dendrimer is generated by the process comprising: providing a G5 PAMAM or POPAM dendrimer; conjugating one or more functional groups to the dendrimer; and acetylating the dendrimer conjugated to one or more functional groups.

In order to render a claim obvious a cited reference must enable one of ordinary skill in the art to make and use the invention.⁴ Applicants submit that the cited references do not enable an acetylated dendrimer comprising one or more functional groups of the claimed invention nor a process for generating the same. In particular, all of the specific examples of Tomalia et al. and Zhou et al. teach dendrimer modifications that increase the reactivity of a dendrimer surface and none describe modification (e.g., acetylation) of a dendrimer that decreases dendrimer reactivity. Thus, each of the cited references fail to provide detail or instruction to one of ordinary skill in the art concerning generation of a dendrimer comprising an acetylated generation 5 (G5) polyamideamine (PAMAM) or polypropylamine (POPAM) dendrimer comprising one or more functional groups.

Thus, the cited references fail to teach, suggest or enable the claimed invention.

2) The Examiner Does Not Provide Objective Evidence Suggesting the Claimed Invention and Actually Cites to References That Teach Away From the Claimed Invention

⁴ See *Beckman Instruments v. LKB Producter AB*, 892 F.2d 1547, 1551; 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).

The references cited in the current Office Action not only fail to teach or suggest the claimed invention, they actually teach away from the claimed invention.⁵ Applicants contend that one of ordinary skill in the art immediately appreciates that Tomalia et al. and Zhou et al. teach dendrimer surface modifications that **increase** a dendrimer's ability to react with and/or to be conjugated to other moieties (e.g., surrounding compounds).

For example, in the current office action, the Examiner alleges that

"Zhou et al teaches that functionalizing dendrimers with various end groups that can be linked to other chemical moieties and enhance surface properties of dendrimers for drug carriers and gene transfer agents is well known in the art. Zhou et al specifically teaches acylation of dendrimers with acetic anhydride, which allows the dendrimer to become water soluble and linked to an active agent, with potential for a carrier as an antitumor drug (pg. 254-255, Conclusion)." (Office Action page 6).

Furthermore, surface reactions disclosed by Tomalia et al., in addition to being "used in various combinations to create stratified dendrimers with differentiated generations possessing different segment lengths, different branch-juncture multiplicities, and varied hydrophobicity[,]"⁶ existed for subsequent functionalization of the dendrimer. In other words, the surface reactions disclosed by Tomalia et al. existed for generating dendrimers with reactive groups for conjugation to other moieties. For example, Tomalia et al. disclose surface reactions of a dendrimer that "can be used to produce linear nonbranched dendrimer segments which possess interior OH groups. Since the OH groups do not participate in Michael addition reactions, these hydroxylated segments can be subsequently functionalized."⁷

Thus, one of ordinary skill in the art immediately appreciates that Tomalia et al. and Zhou et al. teach dendrimer surface modifications that increase the dendrimer's ability to react with and/or to be conjugated to other moieties (e.g., surrounding compounds). In stark contrast, the claimed compositions of the present invention comprise dendrimers (e.g., conjugated to one or more functional groups) comprising charge neutral capping acetyl groups that neutralize reactivity of the dendrimers.

⁵ According to the MPEP, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See *In re Geisler*, 116F.3d 1465, 1471, 43 USPQ3d 1362, 1366 (Fed. Cir. 1997). MPEP §2144.05(III). Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (See MPEP §2141.02).

⁶ See Tomalia et al., page 164, right column, fourth sentence of the last paragraph beginning on page 164 and continued on page 165.

⁷ See Tomalia et al., page 165, left column, lines 1-5.

Thus, Applicants respectfully submit that various teachings of Tomalia et al. and Zhou et al. lead one of ordinary skill in the art away from an acetylated dendrimer defined by Claims 26-52 of the present invention.

3) The Cited References Do Not Provide a Reasonable Expectation of Success for Generating the Claimed Invention

In addition to teaching away from the present invention, the cited references fail to provide a reasonable expectation of success for generating the claimed invention. Applicants respectfully submit that the Examiner has improperly utilized hindsight reconstruction of the claimed invention in an effort to support the allegation that the claimed invention is prima facie obvious.

The Supreme Court in *Graham* established specific steps for a non-obvious analysis: (1) determine the scope and content of the prior art; (2) evaluate the differences between the prior art and the claims at issue; and (3) determine the level of ordinary skill in the art.⁸ "Against this background, the obviousness or non-obviousness of the subject matter is determined."⁹ These *Graham* steps provide a subjective analysis of whether an invention was obvious **at the time it was made**. Objective evidence, termed "secondary consideration" evidence, that an invention was not obvious at the time it was made also may be introduced.¹⁰ Such secondary consideration evidence could include, for instance, the commercial success of an invention or that the invention filled a long-felt need. The Supreme Court recognized the use of secondary consideration evidence in *Graham* in an effort to "guard against slipping into use of hindsight."¹¹ The Federal Circuit has followed this holding and ruled that it is "error to exclude [secondary consideration] evidence from consideration."¹² In an effort to achieve this goal, courts have recognized a variety of types of secondary consideration evidence, including: long-felt need,¹³ commercial success,¹⁴ the failure of others to achieve the invention,¹⁵ licensing by others,¹⁶ and unexpected results or advantages.¹⁷

⁸ See *Graham*, 383 U.S. at 17.

⁹ *Id.*

¹⁰ *Id.* at 17-18.

¹¹ *Id.* at 36 (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (1964)).

¹² *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983).

¹³ *Ecolchem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000)

¹⁴ *Id.* at 1377-1378.

Thus, the non-obvious standard of § 103(a) requires the Examiner to make a historical judgment: whether the invention would have been obvious **at the time the invention was made** in the past. To reach a proper non-obvious conclusion, the Examiner must not only step backward in time to a moment when the invention was unknown, but also avoid letting knowledge that the invention was achieved affect his or her decision about whether it was obvious at the time it was achieved.¹⁸ The courts have recognized that meeting this standard "requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."¹⁹

In an effort to preclude such an improper result, the Federal Circuit requires that the non-obvious analysis be conducted viewing the invention as a whole.²⁰ Using "'hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention'"²¹ or conducting a "reference-by-reference, limitation-by-limitation analysis" fails to demonstrate how the invention is obvious in light of prior art.²² Similarly, the Examiner **may not use the invention as a blueprint for linking together pieces of prior art** in order to find the invention obvious.²³ The Federal Circuit has referred to using the invention as a "blueprint for piecing together the prior art . . . [as] the essence of hindsight."²⁴

Applicants respectfully submit that the Examiner has improperly utilized hindsight reconstruction of the claimed invention in an effort to support the allegation that the claimed invention is prima facie obvious. Applicants contend that, at the time the invention was made, there existed no explicit or implicit teaching or suggestion or motivation to modify or combine

¹⁵ *Id.* at 1378-1379.

¹⁶ *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed.Cir. 2000).

¹⁷ *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1382-83 (Fed.Cir. 1986).

¹⁸ *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966)

¹⁹ *In re Dembiczak*, 175 F.3d at 999 (emphasis added); see also *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983) ("It is difficult but necessary that the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.").

²⁰ See *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004).

²¹ *Ecolchem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (quoting *In re Fine*, 837 F.2d 1071, 1075 (1988)).

²² *Id.*, at 1374

²³ *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

²⁴ *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)

elements present in the art to generate the claimed invention. Furthermore, as described above, knowledge generally available to one of ordinary skill actually leads away from the present invention.

Applicants submit that the Examiner fails to acknowledge or to examine the state of the art at the time of the invention. For example, the Examiner ignores determining whether one of ordinary skill in the art **at the time of the invention** would have been motivated to make such a modification or whether such a modification would have been expected to generate a functional dendrimer. In particular, the Examiner fails to acknowledge or to discuss how the allegedly obvious acetylation would impact, alter or change dendrimer reactivity or whether acetylation of a dendrimer would even be possible post conjugation of the dendrimer to one or more functional groups (e.g., whether any reactive amino termini remained post conjugation). Furthermore, the Examiner fails to address whether one of ordinary skill in the art at the time of the invention would have expected acetylation of a dendrimer to produce a functional dendrimer.

Tomalia et al. in fact teach the unpredictable nature of dendrimer chemistry. For example, Tomalia et al. describe that

"dendrimers can be controlled by appropriate choices of N_c , N_b and branch-segment lengths l , as well as the flexibility and shapes of the branch segments. A qualitative overview of how N_c and N_b may affect interior topology is provided by the two-dimensional projections shown in Figure 45. Because of the variety of possible heteroatoms or functional groups, it is easy to conceptualize many new endo-receptor microenvironments, which would resemble multiarmed entities described by Vogtle and Weber,^[119] Suckling,^[120] and Menger^[121] or pseudo-macrocyclic (cryptate-like) prototypes.^[9, 13, 34-36] **Very little is known about these dendrimer properties** although it has been noted that ester-terminated PAMAM dendrimers form deep blue complexes with CuSO_4 solutions, whereas NH_2 -terminated homologues produce deep purple solutions.^[62] The well-known coordination properties of the amide bond, which lead to the formation of metal-ion complexes,^[122] **should make this a very rich area for further investigation.**²⁵

Additionally, in contrast to charge neutral capping via acetylation of a dendrimer comprising one or more functional groups of the present invention, Zhou et al. suggest that acetylating a dendrimer increases its reactivity which allows the dendrimer to become water soluble and linked to an active agent.

²⁵ See Tomalia et al., page 163, last paragraph of right column continued on top of left column of page 164, emphasis added.

The unpredictable nature of the present invention is exemplified by the Examiner's nearly opposite allegations regarding the cited references and the alleged obviousness of the claimed invention. For example, in the Office Action mailed January 26, 2007, the Examiner argued that "it would have been an obvious choice by one skilled in the art to change the functional group from a reactive and highly positive charged amine terminated dendrimer to a neutral acetyl terminated dendrimer if one did not want the dendrimer reacting with surrounding negatively charged compounds (Office Action mailed January 26, 2007, page 4). This is in contrast to the Examiner's reference to Zhou et al. and the allegation that

"Zhou et al teaches that functionalizing dendrimers with various end groups that can be linked to other chemical moieties and enhance surface properties of dendrimers for drug carriers and gene transfer agents is well known in the art. Zhou et al specifically teaches acylation of dendrimers with acetic anhydride, which allows the dendrimer to become water soluble and linked to an active agent, with potential for a carrier as an antitumor drug (pg. 254-255, Conclusion)." (Office Action page 6).

The Examiner's allegations exemplify the unpredictable nature of the invention and the lack of a reasonable expectation of success for generating the claimed invention to one of ordinary skill in the art. In fact, as cited above, Tomalia et al. teach the unpredictable nature of dendrimer chemistry (e.g., surface chemistry and solubility).

Thus, the Examiner has failed to cite objective evidence from the cited references, or from anywhere, that modification of a dendrimer conjugated to one or more functional groups via acetylation would generate a functional dendrimer (e.g., that an acetylated dendrimer would in fact be useful (e.g., soluble)) or that addresses the state of the art at the time of the invention (e.g., the importance of a dendrimer possessing reactive amino termini (e.g., for conjugation to a therapeutic agent and other functional groups)).

Applicants submit, for the sake of argument, that even if the references provide a generalized teaching to try to modify the surface chemistry of a dendrimer using acetylation, that this is nothing more than an invitation to experiment and does not render obvious Applicants' invention.

Thus, the Examiner has failed to cite to objective evidence rendering *prima facie* obvious a composition comprising an acetylated generation 5 (G5) polyamideamine (PAMAM) or polypropylamine (POPAM) dendrimer wherein the acetylated dendrimer comprises one or more functional groups, wherein at least one of the functional groups comprises a therapeutic agent,

nor such a composition wherein the acetylated dendrimer is generated via a process comprising: providing a G5 PAMAM or POPAM dendrimer; conjugating one or more functional groups to the dendrimer; and acetylating the dendrimer conjugated to one or more functional groups.

Accordingly, the claims are not rendered obvious over Tomalia et al. and Zhou et al. in view of Malik et al. Applicants respectfully request the Examiner withdraw rejection of Claims 26-35 under 35 U.S.C. § 103(a).

B) The Claims are Not Obvious over Tomalia et al. and Zhou et al in View of the '166 Patent

The Examiner alleges that

“It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the chemotherapeutic agent, cisplatin into a PAMAM dendrimer with the functional groups as described by Tomalia et al and Zhou et al, since Tomalia teaches dendrimer metal complexes and Zhou et al teaches complexes with active agents (fluorouracil and antitumors). One of ordinary skill in the art would be motivated by the success of the results of Malik et al who found that the complexed dendrimer-Pt reduces toxicity and increases solubility of cisplatin to combine with the teachings of Tomalia et al. Thus, it would have been *prima facie* obvious to combine the teachings of Malik et al with Tomalia et al and Zhou et al to obtain a drug containing dendrimer with the functional group of choice.” (Office Action, pages 7-8).

This allegation is not factually or legally supportable.

Zhou et al. does not teach, describe or suggest a composition with active agents (fluorouracil and antitumors).

Applicants submit that in addition to being impermissible hindsight reconstruction of the claimed invention, this allegation fails to consider the state of the art at the time of the present invention (e.g., the importance of a dendrimer possessing reactive amino termini (e.g., for conjugation to a therapeutic agent and other functional groups)). The allegation also fails to cite objective evidence providing the motivation to modify a dendrimer via acetylation and whether there would have been a reasonable expectation of success of generating a functional (e.g., soluble and/or stable), acetylated dendrimer comprising one or more functional groups. Furthermore, as described above, the cited references teach away from the claimed invention. Applicants contend that the Examiner is impermissibly **using the invention as a blueprint for linking together pieces of prior art** in order to allege the invention obvious.

Accordingly, the claims are not rendered *prima facie* obvious in view of the cited references. Applicants respectfully request the Examiner withdraw rejection of Claims 26-35 under 35 U.S.C. § 103(a).

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608-218-6900).

Respectfully submitted,

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